REMARKS

Upon entry of this amendment, claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48, 52-55, and new claims 57-59 are pending. Applicants reserve the rights to prosecute claims of identical or similar scope in future continuation or divisional applications. Support for the new claim can be found throughout the specification. Support for the amendment to claims 17 and 42 can be found throughout the specification, including at least at paragraphs 31 and 110-114 of the published application. *No new matter has been added.*

In Examiner's request, Applicants hereby clarify for the record that Claims 34 and 35 are pending; and that the status of Claim 31 as of the last response is "Previously Presented" (*i.e.*, no amendment was made to Claim 31 in the response filed on December 10, 2008).

Applicants respectfully request the Examiner to consider the following arguments in view of the amendments to the claims.

Withdrawal of Rejections

Applicants thank the Examiner for the withdrawal of previous rejections set forth under 35 USC § 112, first paragraph and § 102(a).

Rejection Under 35 U.S.C. § 103(a)

Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, and 48 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Stephens in view of Salfeld, den Broeder, further in view of Kempeni (all of record). Applicants respectfully traverse this rejection.

The Examiner appears to disagree with Applicants regarding certain facts concerning the scope and content of the cited art. Since "determining the scope and content of the prior art" is the beginning and basis for obviousness analysis under *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), Applicants first wish to set forth the scope and content of the cited art, and then argue that none of the cited art, either alone or in combination, teaches all the limitations of the presently claimed invention. Thus, the claims are not obvious in view of the cited art.

(1) Stephens does not teach the treatment of arthritis with a single dose of 0.1 mg/kg humanized anti-TNFα antibody such that the arthritis is treated as demonstrable by mean arthritic score (claims 15 and 42), such that at least one symptom selected from the group consisting of joint distortion, swelling of the joints, joint deformation, or ankylosis on flexion is alleviated (claims 15 and 42), or such that the at least one symptom selected from the group consisting of bone erosion, cartilage erosion, inflammation, and vascularity is alleviated (claims 21 and 48)

To support his position, the Examiner cites p327, 1st paragraph of Stephens: "[a]ll patients who received CDP571 scored a reduction in pain scale by week 1" (emphasis added). However, the subjective "pain scale" provided by the patients themselves (see page 326, third paragraph of Stephens) is not relevant to the objective standards recited in the claims. The claimed invention requires that at least one recited symptom - bone erosion, cartilage erosion, inflammation, vascularity, joint distortion, swelling of the joints, joint deformation, or ankylosis on flexion - be alleviated (independent claims 15, 21, 42, and 48). Moreover, the Examiner has provided no evidence of what such a "pain scale" would have measured.

There is no disclosure in Stephens regarding evidence of symptom relief for the 0.1 mg/kg treatment group commensurate with the required elements of the amended claims. Applicants note that Table 2 on page 328 only shows data for the 1 mg/kg and the 10 mg/kg treatment groups. In fact, a careful examination of the Table 2 data reveals that in the 1 mg/kg treatment group, under the symptom "Swollen Joints," the average number of swollen joints failed to decrease, and in fact increased during the treatment period, from 15.0 (pre-infusion) to 16.5 (week 1), 16.0 (week 2), 17.0 (week 4), and 17.0 (week 8). Applicants submit that "Swollen Joints" is the symptom that most closely correlates "mean arthritic score," since the scoring system for mean arthritic score cites swelling deformed joint as a determinant (see page 27, last paragraph of the specification).

With respect to the "pain scale" data itself, Applicants are unable to verify the extent of the alleged pain reduction in the 0.1 mg/kg treatment group, since such data is not shown in Stephens. However, the 1 mg/kg treatment data clearly shows a worsening trend from week 1 to week 8, despite a seemingly lower pain score on week 1 (4.2). In fact, at week 8, the pain score ballooned to 8.3 from the pre-infusion score of 5.5, a 51% increase. The insignificance of the

week 1 pain score, which appears to be the only Stephens data relied upon by the Examiner, is further underscored by the fact that the placebo group also appeared to have a week 1 pain score reduction (from 6.2 to 5.7).

In view of such data, one of skill in the art would conclude that, at 1 mg/kg (which is notably 10-100 times the claimed dose range), the Stephens treatment regimen failed to show that *humanized* anti-TNFα antibody can be used to treat arthritis by alleviating the symptoms recited in independent claims 15, 21, 42, and 48. Moreover, Stephens also fails to show how a *humanized* anti-TNFα antibody can be used to treat arthritis "as demonstrable by mean arthritic score," as required by independent claims 15 and 42.

Applicants also note that, other than relying on the argument that "Stephens teaches the use of *humanized* anti-TNFα antibody to reduce pain scale by week 1 in ***all*** patients," (see above) the Examiner has not provided any other argument against Applicants' "teach-away" argument. Applicants submit that the analysis above further strengthens Applicants' previous "teach away" argument and the statement that "Stephens provides no evidence that a 0.1 mg/kg dose of CDP571 is effective in treating arthritis (to the extent recited in the claims)," partly because it shows the irrelevancy of the week 1 pain scale data - the only data relied upon by the Examiner. Applicants further note that, in the second to the fourth round of CDP571 treatment, the 0.1 mg/kg treatment group was dropped altogether. One of skill in the art would reasonably interpret this as teaching away from using a CDP571 dose lower than 1 mg/kg, certainly as teaching away from using a CDP571 dose lower than 0.1 mg/kg.

(2) Salfeld fails to disclose "a low dose of 0.01 - 0.1 mg/kg at a frequency of not more than once per week"

The Examiner argues that one of skill in the art would have been motivated to replace the humanized CDP571 antibody in Stephens with the fully human antibody in Salfeld, at a dose of 0.1 mg/kg.

However, the claimed invention is not only limited by a low dose range (0.01 - 0.1 mg/kg), but also a low frequency of "not more than once per week." Although Salfeld does recite the broad range of 0.1 - 20 mg/kg, it does so without concurrently reciting a frequency of administration. In fact, the only time an administration frequency is recited with a dose range is

in Example 4, part D, section III (col. 43, lines 6-8), where a thrice a week frequency is used: "[e]ach group received three i.p. injections per week of the indicated treatments" (emphasis added). Therefore, Salfeld fails to disclose the use of any human antibody at both a low dose of 0.1 mg/kg and a frequency of not more than once per week, as recited in all the independent claims.

Furthermore, as argued above, other than the irrelevant and at best questionable "pain score" in the 0.1 mg/kg treatment regimen, Stephens fails to show any relevant data regarding the 0.1 mg/kg treatment regimen using a *humanized* antibody. Even the 1 mg/kg treatment data is marginal at best. Therefore, even assuming for the sake of argument that one of skill in the art would have been motivated to replace the Stephens antibody with a fully human antibody as taught in Salfeld (which Applicants do not concede), the skilled artisan would at best arrive at an effective dose of about 1 mg/kg, not 0.1 mg/kg (and certainly not *below* 0.1 mg/kg).

Due to the disclosure (or lack thereof) in Salfeld, as discussed above, one of skill in the art would have received no guidance from Salfeld to use a low dose of 0.01 - 0.1 mg/kg of fully human antibody at a frequency of not more than once per week, let alone achieving any of the objective treatment standard as recited in the claims.

Since Salfeld fails to teach the requisite low dose and the frequency of administration, Applicants need not address further the "touching range" issue and the associated "unexpected results" argument.

(3) den Broeder does not teach administering D2E7 "in a low dose of 0.01 - 0.1 mg/kg at a frequency of not more than once per week"

The Examiner does not dispute the fact that the minimal dose administered in den Broeder is 0.25 mg/kg. However, the Examiner argues that three of the patients' doses could be successfully titrated down to 0.25 mg/kg per one administration every 2 or 4 weeks. The Examiner then equates this to a dosage regimen of 0.0625 - 0.125 mg/kg per week, and argues that this overlaps the claimed range and frequency. Applicants respectfully disagree for two reasons.

As a first matter, den Broeder does not disclose the exact treatment regimens for the three patients whose dosage levels were titrated down to 0.25 mg/kg. The reference only discloses that all enrolled patients were either administered D2E7 once every two weeks or once every four weeks. Thus, it is entirely possible that all three patients were on the once per two weeks schedule, making the lowest average dose to 0.125 mg/kg per week. Of course, in theory, it may also be possible that at least one of them was indeed on a once per 4 weeks schedule, making his / her average dose to allegedly fall within the claimed range as suggested by the Examiner. As den Broeder fails to provide critical information, the Examiner's argument is based, therefore, on a theoretical *possibility*. Since the obviousness analysis must be based on the *Graham* factual inquiry, Applicants submit that the Examiner's argument is not based on substantial evidence, and thus falls short of the legal requirements mandated under *Graham v. John Deere Co.*

Secondly, for the Examiner's argument above to stand, a high dose (such as 0.25 mg/kg) over a low frequency (such as once per 4 weeks) must be equivalent to a low dose (such as 0.0625 mg/kg) over a higher frequency (such as once per 1 week). However, there is evidence that this may not be true. As the Examiner realizes, Stephens teaches on page 320 that lower doses of antibodies tend to clear faster from circulation (see Figure 1 in Stephens), have a shorter serum half life (see Figure 2 of Stephens), and trigger more pronounced anti-idiotypic antibody reaction (see Figure 3 of Stephens). Therefore, while a single high dose of 0.25 mg/kg may be effective enough to keep the patient's symptoms under check for 4 weeks, cutting this dose by 4 fold (to 0.0625 mg/kg) may instead lead to accelerated clearance of the antibodies from the patient (due to, for example, shortened half life and/or enhanced anti-idiotypic reaction), causing the undesirable "flare up" even before the next low dose of 0.0625 mg/kg is scheduled to be administered one week later.

In any event, den Broeder never actually teaches or suggests the use of a human anti-TNFα antibody "in a low dose of 0.01 - 0.1 mg/kg at a frequency of not more than once per week" as required by the claims, and does not disclose how much lower the combined dosage and frequency can go without completely foregoing the benefit of the treatment.

With respect to Kempeni, Applicants submit that Kempeni does not make up for the deficient teachings of the primary reference (Stephens) alone or in combination with the secondary references (Salfeld and/or den Broeder).

In summary, none of the cited art (taken alone or in combination) teaches or suggests the recited dosage and frequency limitation of Applicants' claims. The humanized antibody regimen disclosed in Stephens uses a dose 10-100 times higher (1 mg/kg) than the recited dose to achieve marginal results. Even assuming for the sake of argument that one of skill in the art would be motivated to replace such humanized antibody in Stephens with the fully human antibody of Salfeld, there is no guidance regarding the dosage level *and* the accompanying administration frequency in Salfeld. den Broeder also does not remedy this deficiency. Therefore, the combined teachings of the cited art fail to disclose all of the limitations of the presently claimed invention, and, furthermore, teach away from the instant invention. A *prima facie* case of obviousness is not established. Reconsideration and withdrawal of the obviousness rejection is respectfully requested.

Rejection Under 35 U.S.C. § 102(b)

Claims 54 and 55 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Le *et al.* (U.S. Pat. No. 6,277,969). Applicants respectfully traverse the rejection.

While not necessarily agreeing with the reasoning of the Office Action, and solely to advance prosecution, Applicants have amended Claims 54 and 55 to delete reference to "infliximab" and "antigen-binding portion thereof." Applicants submit that Le does not anticipate the amended Claims 54 and 55.

With respect to new claims 58 and 59, Applicants note that these new claims describe either a low dose method for treating arthritis or a method for alleviating at least one symptom associates with arthritis, whereby a dose of about 0.5 mg/kg is administered to a subject such that at least one symptom selected from the group consisting of bone erosion, cartilage erosion, inflammation, and vascularity is alleviated. Notably, Le does not describe administration of a dose of about 0.5 mg/kg whereby an arthritic symptom is alleviated, as required by new claims 58 and 59. The Examiner notes that at col. 36, second paragraph, Le describes a range of doses. Le does not teach, however, that such doses would be effective at alleviating a symptom of arthritis as described in new claims 58 and 59. As noted by the Court in *Net Moneyin, Inc. v. Verisign, Inc., et al.*, No. 2007-1565, U.S. Court of Appeals for the Federal Circuit (October 20, 2008), "unless a reference discloses within the four corners of the document not only all of the

limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102." Thus, Applicants submit that new claims 58 and 59 are also not anticipated by I.e.

Reconsideration and withdrawal of the rejection of claims 54 and 55 under 35 U.S.C. § 102(b) are respectfully requested.

Obviousness-Type Double Patenting Rejections

Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, and 48 are rejected under the judicially created obviousness type double patenting rejection over claims 1-7, 17, 19, 20, 36-39, 49, 51, 52, 68, 69, and 70 of U.S. Pat. No. 6,509,015 in view of Stephens, Salfeld, den Broeder, and further in view of Kempeni (all of record).

The Examiner argues that the presently claimed invention is not patentably distinct from the recited claims of the '015 patent, for the reasons set forth above with respect to Stephens, Salfeld, den Broeder, and further in view of Kempeni. Applicants note that the amended claims all require administration of a low dose of a human anti-TNFα antibody, or antigen-binding portion thereof, such that certain symptoms are alleviated. This combination is neither taught nor suggested by the cited references, alone or in combination with one another. As such, Applicants respectfully submit that a *prima facie* case of obviousness has not been established with respect to the amended claims, as described in detail above. As such, Applicants respectfully request that the rejection of claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, and 48 on the grounds of non-statutory obviousness-type double patenting be withdrawn.

Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, and 48 are rejected under the judicially created obviousness type double patenting rejection over claims 1-10 of U.S. Pat. No. 7,223,394 in view of Stephens, Salfeld, den Broeder, further in view of Kempeni (all of record).

The Examiner argues that the presently claimed invention is not patentably distinct from the recited claims of the '394 patent, for the reasons set forth above with respect to Stephens, Salfeld, den Broeder, and further in view of Kempeni. Applicants note that the amended claims

all require administration of a low dose of a human anti-TNFα antibody, or antigen-binding portion thereof, such that certain symptoms are alleviated. This combination is neither taught nor suggested by the cited references, alone or in combination with one another. As such, Applicants respectfully submit that a *prima facie* case of obviousness has not been established with respect to the amended claims, as described in detail above. As such, Applicants respectfully request that the rejection of claims 5-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, and 48 on the grounds of non-statutory obviousness-type double patenting be withdrawn.

Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, and 48 are rejected under the judicially created obviousness type double patenting rejection over claims 17, 41, 79, 86, 103, 110, 115, 122, 127, and 134 of U.S. Ser. No. 11/233,252 in view of Stephens, Salfeld, den Broeder, further in view of Kempeni (all of record).

Since the '252 application has not issued as a patent, this rejection is only proper if it is a *provisional* double patenting rejection. Applicants respectfully request that they be able to address this rejection upon allowance of either the instant claims or those of the '252 application, at which time Applicants will determine the appropriateness to file a terminal disclaimer.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 54 and 55 are rejected for allegedly introducing new matter by reciting "enantercept."

Applicants have amended these claims to correct an obvious typographic mistake, thereby overcoming the new matter rejection. Support can be found throughout the specification, see, for example, page 26, last full paragraph.

Reconsideration and withdrawal of the new matter rejection are respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph - Scope of Enablement

Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, and 48 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to enable to the full scope of the claims.

Firstly, the Examiner argues that one cannot practice the invention claimed in claims 34, 35, and 45 because the recited D2E7 antibody is not "readily available to the public" and is not "obtainable by a repeatable method set forth in the specification."

Applicants respectfully submit that D2E7 is commercially available as HUMIRA® (adalimumab) (see, *e.g.,* http://www.humira.com/), and therefore is available to the public. As described in M.P.E.P. § 2104.01,

> [t]here are many factors that may be used as indicia that a biological material is known and readily available to the public. Relevant factors include ***commercial availability***, references to the biological material in printed publications, declarations of accessibility by those working in the field, evidence of predictable isolation techniques or an existing deposit made in accordance with these rules. (Emphasis added).

Accordingly, based on the knowledge in the art at the time of filing and the public availability of D2E7, in combination with the teachings of the instant specification, Applicants submit that one of ordinary skill in the art could make and use the claimed D2E7 antibodies in accordance with the claimed methods.

Secondly, the Examiner questions the efficacy of D2E7 at 0.01 mg/kg, because Figures 1 and 4 allegedly relate to mean arthritis score, not bone / cartilage erosion; because the data in the specification allegedly fails to show consistent effect in the tg197 mouse model for RA (citing large data error bars); because some data points in the 0.01 mg/kg treatment curve appear to represent "greater" mean arthritis score; and because the figures show the results obtained after 10 consecutive treatments, etc. Notably, the Examiner acknowledges enablement with respect to the claimed invention with respect to the dose of 0.1 mg/kg (see page 12, last paragraph of Office Action).

Applicants submit that, although Figures 1 and 4 pertain to mean arthritis scores, Figure 5 clearly addresses the limitations recited in independent claims 21 and 48 and dependent claims 17 and 43.

Applicants have also amended independent claims 15, 21, 42, and 48 to further clarify the subject matter claimed. Support can be found throughout the specification, such as the first full paragraph of page 28 and the first full paragraph of page 29. See also Figures 1, 4, and 5.

Although Applicants do not necessarily agree with the reasoning of the Office Action, Applicants submit that, with these amendments, the comments in the Office Action regarding greater mean arthritis score in some data points becomes moot. Moreover, Applicants respectfully submit that amended claim 15, 48, and new claim 57 are commensurate with the scope of claim indicated as enabled by the Examiner.

In view of the forgoing, Applicants submit that the claims as amended are enabled to their full scope. Reconsideration and withdrawal of the enablement rejections are respectfully requested.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance. If a telephone conversation with Applicant's Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 449-6500.

The Commissioner is hereby authorized to charge any fees associated with the filing of this communication to our Deposit Account No. **50-4876**, under Order No. **117813-99302**, from which the undersigned is authorized to draw.

Dated: August 18, 2009

Respectfully submitted,

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